Modafinil—Medical Considerations for Use in Sustained Operations

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An understanding of the consequences of sustained operations involving prolonged sleep deprivation is important to the military. Losses in cognitive performance of the order of 30% after one night and 60% after two nights of sleep loss have been shown to occur in several studies. Napping strategies have been proposed as one coping strategy for these performance decrements. An alternate solution is the use of stimulants. Modafinil may offer a safer alternative to more commonly used psychostimulants. It has been shown to counteract the effects of sleep deprivation with fewer side effects than amphetamine. Recent studies on the effects of modafinil during sleep deprivation are reviewed and compared with those of other stimulants such as amphetamine and caffeine, and to prophylactic naps. Recommendations are proposed for the use of modafinil in sustained military missions. For missions of about 24 h, modafinil is preferable to naps. For longer missions, naps should be considered, along with the concomitant use of modafinil to help maintain performance levels. The authors discuss apparent 'overconfidence' and hyperthermia-inducing effects of modafinil, and advise that these effects be taken into account if modafinil is to be used in any mission conducted in the field or in hot environments. It is also recommended that individual sensitivity to the drug should be tested before any mission of a sustained nature, especially if it involves small operational groups or combat aircrew, where the impact of such effects on individuals would be more critical.

Keywords: modafinil, amphetamine, sleep deprivation, hyperthermia, sustained operations.

THE CONCEPT OF SUSTAINED military operations requires that modern combat be conducted night and day, which will result in significant sleep deprivation (SD). Sleep deprivation is associated with increasing levels of subjective fatigue, deterioration in mood, and impaired cognitive performance and decision making (15). This can impact significantly on military operations. When SD is coupled with intense cognitive challenges extended over 60 to 64 h of sustained operations, performance decrements of 30 to 40% can occur during the first night of SD, and 60 to 70% the following night without sleep (1). Furthermore, SD increases sleep propensity, and it is necessary to sleep about 14 h in order to recover from 36 to 60 h of continuous wakefulness (8,11).

To counter the degradation in mental performance during continuous wakefulness, naps of 2 h have been shown to be effective in partially recuperating performance levels, especially when SD exceeds 24 h (26). However, naps have a major drawback as they are often followed by sleep inertia immediately on awakening, which can prejudice mental performance for up to 2 h following a nap. This can be critical in certain operational conditions such as command and control, decision-making scenarios, and the operation of complex weapon systems and platforms.

The requirement to conduct sustained operations without sleep has led to the search for drugs capable of maintaining wakefulness with minimal side effects. Amphetamine has been widely used as a stimulant in military operations (16), but its use is limited by side effects such as cardiovascular disturbances, psychiatric problems, addiction, drug tolerance, and disruptions in sleep recovery. Caffeine, in doses large enough to improve vigilance, commonly produces irritability, nervousness, diuresis, and tremor (32). Although slow-release caffeine is said to have few of these disadvantages and has been used to counteract jet lag (22,27), no study to date has assessed its efficacy during sustained SD.

Within the last decade, modafinil, originally developed to counter narcolepsy, has proven to be an effective eugregoric drug that maintains normal wakefulness, vigilance, and performance under conditions of extended wakefulness. Unlike amphetamine, which acts by stimulating the central nervous system, it has been hypothesized that modafinil acts by inhibiting sleep mechanisms originating from the anterior hypothalamic area (23). Thus, one of the advantages of modafinil over amphetamine is that it permits sleep in the case of an interrupted mission or when naps are allowed. It appears to be non-euphoric and non-addictive, with fewer side effects than amphetamine or caf-

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feine (24). As a result, modafinil has received increasing attention as a potential alerting substance during sustained military operations (7).

The intent of this medical review of recent experimental studies on modafinil is to bring to the attention of military medical and operational personnel not only the benefits of modafinil over other commonly used stimulants, but also the potential side effects that have been observed by many investigators as well as ourselves, particularly under simulated operational scenarios. We conclude with recommendations and cautions for the usage of modafinil in operational scenarios.

Effects on Cognitive Performance and Sleep

Together with investigations conducted by other teams, we have found that the use of modafinil by military personnel under conditions that involve significant SD offers advantages for performance and sleep over other stimulants. In one trilateral study between Canada, France, and the U.S., the effectiveness of modafinil and d-amphetamine vs. placebo in maintaining and recuperating declines in cognitive performance was examined during 64 h of SD (30). The experimental paradigm consisted of subjects working continuously on a large battery of cognitive tasks for 64 h without rest, except for 15-min breaks every 2 h. Either d-amphetamine (20 mg), modafinil (300 mg), or placebo were administered after 17.5 h of wakefulness at 2330 of the first night, a second dose given 30 h later at 0530 after 47.5 h without sleep, and finally a third dose at 1530 after 57.5 h of wakefulness. The rationale for the placement of the third dose was to examine the effects of the drugs on subsequent recovery sleep (11,30). The placement of the first two drug treatments coincided with the times at which 2-h naps were given as a countermeasure in an earlier study conducted under the same experimental conditions (26).

Decrements of 30% in cognitive performance were found during the first 24 h after placebo administration, increasing to 55% after 48 h without sleep. In both the amphetamine and modafinil groups, only a 5% to 10% decline in performance was seen after the first 24 h of sleep loss. However, performance was comparable to that of the placebo group after 48 h of SD. The second drug treatment, given after 48 h of SD, improved performance over the next 10 h by 20% to 30% above baseline levels for the two drugs. No differences were observed between modafinil and d-amphetamine. During the debriefing, subjects reported experiencing a heightened arousal when on amphetamine whereas with modafinil, they felt less fatigued.

Recovery sleep on the first night after placebo was characterized by rebounds in slow-wave sleep and REM. The first half of recovery sleep was dominated by slow-wave sleep, whereas REM recovery was distributed evenly across REM sleep episodes. After amphetamine, both the first and second nights of recovery sleep were disrupted, with increased sleep latencies, intra-sleep wakefulness, decreased total sleep time and sleep efficiency. REM sleep was also decreased along with a longer REM sleep latency. Recovery sleep after modafinil was similar to that of placebo, with rebounds in both slow-wave sleep and REM sleep and fewer disturbances than seen with amphetamine. However, the length of recovery sleep was shorter after modafinil, suggesting that the need for recovery sleep after modafinil was less than that in the other two groups (11). The study concluded that modafinil offered a better and potentially safer alternative to amphetamine for combating the effects of sleep loss on performance.

A comparison of the effectiveness of modafinil and amphetamine found in this study to that found in a previous study of 2-h naps administered at the same times as the drug treatments (26), shows that both modafinil and amphetamine taken at 2330 on the first night of SD maintain performance longer than a 2-h nap taken at the same time (29). However, after 48 h of SD, a 2-h nap inserted at the circadian nadir of the second night without sleep is as good or more effective than modafinil or amphetamine given at approximately the same time. Therefore, it appears that both modafinil and amphetamine are more effective than naps in maintaining cognitive performance for short sleep-deprived missions, but for longer missions, implementation of sleep-wake management strategies, if possible, might be a preferable alternative to the use of drugs. Alternatively, a 2-h nap followed by a dose of modafinil [illegible] more effective in recuperating performance than either strategy alone (7). In this respect, Bonnet et al. (9) found that performance could be recuperated for a 24-h period by giving subjects 200 mg of caffeine after a prophylactic nap compared with a nap alone, and suggested that pairing a nap with an alerting substance may be additive. This suggestion requires confirmation by further studies.

A subsequent study was carried out to assess whether there was a dose-related effect of modafinil in combating fatigue and degradations in alertness and cognitive performance over 64 h of SD (4). Three different doses of modafinil (100 mg, 50 mg, 16.7 mg) were administered every 8 h starting at 2000 on the first night. A dose of 100 mg taken every 8 h (a total of 300 $mg \cdot d^{-1}$) effectively maintained cognitive performance near initial levels during the entire SD period. A dose of 50 mg every 8 h (150 $mg \cdot d^{-1}$) was only moderately effective, and the lowest dose of 16.7 mg every 8 h (50 $mg \cdot d^{-1}$) was no different from placebo (4). The quality of recovery sleep and sleep duration after the two larger doses of modafinil (12) was similar to that found in the previous study (11).

Others have also reported positive effects on performance of modafinil. Brun et al. (10) found that a dose of 300 mg of modafinil administered at 2200 and again at 0800 (600 mg over 10 h) on the first night of 36 h of SD improved response time and performance. Although Lagarde and Batéjat (21) observed some effects on performance after 200 mg modafinil repeated every 8 h over 60 h of SD, these were only marginally significant. Caldwell et al. (14) found that three 200-mg doses of modafinil given every 4 h beginning at 2300 attenuated sleep loss effects on flight maneuvers in pilots flying helicopter simulators. A recent study compared single doses of modafinil (100, 200, or 400 mg) to caffeine (600 mg) administered after 42 h of SD on performance and

alertness (32). Doses of 200 and 400 mg of modafinil significantly improved performance and alertness, and were comparable to those found with 600 mg of caffeine. Both caffeine and the high dose of modafinil (400 mg) also increased core temperature. Therefore, modafinil is able to maintain and/or restore mental performance during SD across a wide range of tasks and doses without significantly affecting the quality of recovery sleep.

Ergogenic and Thermogenic Effects

Other potentially important effects of modafinil are its ergogenic and thermogenic properties. Jacobs and Bell (19) demonstrated that a dose of modafinil of 4 mg · kg $^{-1}$ body weight (about 300 mg) vs. placebo prolonged the time to exhaustion during high intensity submaximal exercise. Although oxygen uptake and respiratory parameters were similar between the modafinil and placebo groups, subjective self-ratings of perceived exertion by the subjects after the completion of the exercise were lower for modafinil than placebo, even though subjects were blind as to how long they had exercised. A potentially important property of modafinil is its effects on thermoregulation. Studies by Brun et al. (10) and Pigeau et al. (30) have shown that a 300 mg dose of modafinil given in the late evening (2300) suppressed the normal circadian fall in core temperature during the early morning hours. A subsequent dose at 0800 h the following morning increased core temperature by approximately 0.4°C for the remainder of the sleep-deprived day relative to the placebo (10). This thermogenic effect of modafinil raised the question whether under heat stress conditions, modafinil may actually degrade cognitive performance (17), rather than maintain it. Secondly, it may also limit physical work capacity in a hot environment by predisposing individuals to a greater risk of exertional heat injury

To date, most of the research evaluating the efficacy of modafinil has focused on normal thermal environments under physically sedentary conditions. With increasing military operations in tropical areas, there is a risk that modafinil may lead soldiers to over-exertion and hyperthermia, with the potential of heat exhaustion or heat stroke. This could place the modafinil user in a potentially hazardous situation.

To address this concern, we designed a protocol with the intent of simulating operational conditions in hot environments as closely as feasible in a climatic chamber (13). The study consisted of 40 h of SD in a climatic facility at a temperature of 30°C and 50% relative humidity. During the SD period, subjects performed three bouts of physical exercise on a treadmill for 2 h at 65% of their $\dot{V}O_{2peak}$ at 1530–1730 (after 9 h of wakefulness), 0330–0530 (21 h of wakefulness), and 1530–1730 of the second day (33 h of wakefulness). Thus, subjects were exposed to a multi-stressor environment of SD, heat, and physical exercise. Full details of this protocol have been described in two recent publications (5,25). In this study, a low-dose regime of modafinil, typical of that employed in the clinical treatment of narcolepsy, was used to assess the ability of modafinil to maintain performance throughout the 40-h SD period. Modafinil (100 mg) or placebo was administered at 0700, 1300, and 0100 of the first day of SD in the climatic chamber (300 mg of modafinil over a 24-h period), and at 0700, 1300, and 1900 of the second day.

A thermogenic effect of modafinil was evident throughout the period in the chamber, core temperatures (approximately + 0.2°C) and skin temperatures (ca., +0.47°C) being significantly higher than with placebo (25). Modafinil also had a differential effect on core temperature during exercise. These data demonstrated that modafinil produced an additional thermal stress in our subjects, who were already under a thermal stress in the warm environment. However, our subjects did not exercise to exhaustion and despite core temperatures in excess of 39°C, no one became ataxic or exhibited any symptoms of exertional heat illness. Nevertheless, the higher core temperature responses during the last two exercise sessions after modafinil ingestion are consistent with an earlier onset of exertional fatigue and associated symptoms of heat illness. Whether this effect would be magnified if the initial dose was increased and/or administered at a different time of day is not known. It has been shown by others that resting core temperature is greater following a 300 mg dose administered late in the evening (10).

Despite significant increases in core body temperature, cognitive performance was largely unaffected by the warm environment per se. Although sleep loss induced a general reduction in cognitive performance, this was largely, but not completely, eliminated by modafinil (5). As found in previous studies under sedentary conditions (11,12), modafinil shortened sleep duration during the first recovery night, but the debt in slow-wave sleep was not fully repaid after only one night of recovery sleep. This suggests that the administration of modafinil under conditions of exercise, heat, and SD, delays the sleep recovery process (13).

Side Effects of Modafinil

Although the above discussion demonstrates that modafinil is an effective countermeasure to the detrimental effects of sleep loss, it does exhibit adverse reactions in some individuals under certain conditions and dosages. It has a dose-dependent effect on anxiety, insomnia, headaches, palpitations, and blood pressure at doses of 200–800 mg · d^{-1} in healthy males. The single dose of 300 mg can antagonize resting tremor (31) and decrease the efficiency of communicated speech (6). Caldwell et al. (14) using a dosing regime of 3 × 200 mg of modafinil over 8 h in sleep-deprived aviators reported symptoms of increased heart rate and nausea, and less frequently, dizziness, headaches, heartburn, jitteriness, and nervousness. Wesensten et al. (32) employed doses of 100, 200, and 400 mg of modafinil in sleep-deprived subjects and found an increasing frequency of adverse symptoms (heart pounding, nausea, jitteriness, and shaking) with dose. An increased frequency of urination, headaches, and hallucinations has been reported in some sleep-deprived subjects ingesting a dose of 300 mg (29,30).

In our recent thermal/exercise/sleep-deprivation study (5,13,25), we began with an initial dosing regime

of 3 × 200 mg modafinil every 24 h based on the findings of Brun et al. (10) who did not report any adverse effects with a dose of 200 mg in resting subjects. However, our first subject on 200 mg experienced severe vomiting after the first exercise session and was released from the experiment. A second subject expressed concerns about feelings of an increasing and irregular heart rate on the second day of the experiment. As a result of these undesirable reactions to the drug exhibited by our first two subjects, the protocol was modified such that the remaining subjects received a reduced dosage schedule of 3 × 100 mg (total of 300 mg · d^{-1}). With the exception of one subject who experienced nausea and vomiting after exercise, none of the other subjects reported any adverse effects on this modified dosage schedule.

An interesting effect found by Baranski and Pigeau in SD subjects taking single doses of 300 mg of modafinil was a consistent tendency for overconfidence about 2 h after drug ingestion (3). This was determined by comparing each subject's assessment with his or her actual performance (2). This raised concerns that modafinil may impair an individual's ability to self-monitor, such that one could adopt strategies that could compromise his or her safety. However, in our multi-stressor study (heat, exercise, and SD) employing a lower dosage level (3 × 100 mg · 24 h^{-1}), we found no evidence of an overconfidence effect using the same tests as in the earlier study by Baranski et al. (5). It appears, therefore, that the overconfidence effect may be dose-related. Given modafinil's generally effective properties in maintaining cognitive performance under a variety of environmental conditions, we feel that at a dosage schedule of 3 × 100 mg per 24 h provides a relatively safe and effective countermeasure to the development of cognitive fatigue under a combination of SD, thermal, and physical stresses.

Recommendations on the Use of Modafinil in Military Operations

1. Modafinil can be used to effectively counteract the performance decrements that occur in individuals working under sustained operational scenarios without sleep. It is non-addictive and does not result in drug tolerance. However, one must take into account the full spectrum of environmental and operational stresses under which it may be used, and be aware of possible side effects that might impact on individual performance.

2. A dosage of 100 mg administered every 8 h to a maximum dosage of 300 mg · d^{-1} is recommended to maintain cognitive performance and alertness with minimal side effects. Single doses of 200 to 300 mg, although also effective, may be associated with a higher incidence of adverse side effects.

3. One should be aware of the potential consequences of any overconfidence effect that might develop after large doses of modafinil. However, a dose schedule of 3 × 100 mg · 24 h^{-1} does not appear to have any antagonistic effect on the perception of one's own cognitive abilities.

4. For sustained operations of up to 24 h without sleep, modafinil (100 mg of modafinil, administered in the evening and again after 8 h) is a more effective countermeasure than a nap in maintaining performance over a sleepless night.

5. For sustained operations longer than 24 h, a 2-h nap taken at the circadian nadir of the second night has been shown to be more effective than drug treatment. However, a nap followed by modafinil may maintain performance at a higher level than either taken alone.

6. Modafinil can be administered to military personnel even when napping is allowed or in the event of an interruption of the mission, as sleep processes are minimally affected by modafinil even when taken 30 min before sleep.

7. Troops using modafinil under hot operational conditions should be made aware of the potential risks of heat exertion injury. Although the elevations in core temperature after modafinil were not large under our experimental conditions and doses, this does not rule out the risk of exertional heat injury in operational scenarios where sleep-deprived personnel must perform prolonged exercise in hotter climates.

8. Individual susceptibility to the potential adverse effects of modafinil should be identified prior to any operational mission, especially in combat aircrew and Special Forces.

Concluding Comments

Although the studies described in this paper have been limited to a maximum of 64 h of SD, the question remains as to how long one could function on only modafinil, or a combination of naps and modafinil. If according to the hypothesis of Pigeau (28) that modafinil does not stimulate the pre-frontal cortex, and if the pre-frontal cortex is particularly sensitive to fatigue (18), then it would not be safe to remain awake using modafinil alone for longer than 60–64 h. Simple, well learned tasks may not be affected very much (i.e., tasks not involving the pre-frontal cortex), but anything requiring judgment may be compromised. The more interesting question is how long somebody can operate effectively using both modafinil and napping.

In theory, a nap that allows slow-wave sleep should be beneficial to alleviating pre-frontal cortex fatigue. Then, if modafinil is taken after naps to get rid of the feelings of sleepiness, it is possible that one could last for at least 5 to 10 d. If the nap was at least 3.5–4.5 h (uninterrupted) in a 24-h period so that Horne's notion of core sleep (18) is satisfied, one could probably last weeks with a combination of naps plus modafinil. All of this is speculation, however, and needs to be proven experimentally.

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14. ABSTRACT

(U) Modafinil is a new stimulant, which has been thought to serve as a countermeasure for alertness and performance decrements due to sleep deprivation, especially in military operational conditions. The authors review the effects of modafinil under sedentary conditions and simulated operational-like environments. They propose a doctrine for the use of modafinil and nap strategies in military missions involving sleep deprivation. In brief, for missions shorter than 40 hours, the use of modafinil is preferable to napping strategies. The authors identify the hyperthermic-inducing effects of modafinil, and recommend that this be taken into account in any missions conducted in hot environments. For longer missions, nap strategies should be considered, along with the potential concomitant use of modafinil to help maintain performance levels. Furthermore, individual sensitivity to the adverse reactions to the drug should be tested before any mission of a sustained nature.

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(U) modafinil; sleep deprivation; hyperthermia; sustained operations